### Will Avilamycin Convert Ziracine into Zerocine?

**To the Editor:** Dr. Courvalin urges that avilamycin be prospectively banned as an antibiotic growth promoter to prevent the development of bacteria cross-resistant to the potential human-use product evernimicin (1). Elanco Animal Health, the manufacturer of avilamycin, would like to clarify the situation with respect to avilamycin and everninomicin. It should be noted that there is incomplete cross-resistance in that enterococci resistant to avilamycin exhibit only decreased susceptibility, not complete resistance, to everninomicin (2). Dr. Courvalin's recommendation has become moot, since Schering-Plough has discontinued clinical development of Ziracin, as announced in early May 2000, "because the balance between efficacy and safety did not justify further development of the product" (http://www.sch-plough.com/news/research/2000/050500.html). Thus, avilamycin actually remains in compliance with the Swann principles. In addition, the Scientific Committee on Animal Nutrition, which advises the European Union Commission, released its assessment of the potential impact from cross-resistance in late April 2000 (http://www.europa.eu.int/comm/food/fs/sc/scan/out48_en.pdf) and concluded that, although transfer of resistant bacteria–and presumably resistance genes–from animal to human bacteria is possible, the magnitude of the transfer with avilamycin resistance was not possible to predict. In part, this conclusion reflected the early developmental status of Ziracin and a few reports of clinical experience. An extensive survey of Ziracin showed that 100% of 4,208 enterococcal isolates from patients in 27 European countries were susceptible (3). Another survey of Ziracin showed that 99.5%-100% of 6,030 isolates of methicillin-resistant *Staphylococcus aureus/epidermidis*, enterococci, streptococci, and pneumococci from 33 laboratories around the world were susceptible (4). Avilamycin has been used in animal production in many of the countries from which these clinical isolates originated. To fairly balance a preemptive precautionary action against a currently marketed animal use product and a human clinical candidate, the World Health Organization Global Principles recommended that such an action be initiated only when the human clinical candidate dossier is submitted for regulatory approval, to ensure that the candidate will indeed enter the marketplace. (Use of antimicrobial growth promoters that belong to classes of antimicrobial agents used or submitted for approval in humans and animals should be terminated or rapidly phased out in the absence of risk-based evaluations.) [http://www.who.int/emc/diseases/zoo/who_global_principles.html#Purpose]). This recommendation also acknowledges, in accordance with the Swann Principles, that antimicrobial agents intended for nonhuman use can be used in animal production. The modification by the pharmaceutical industry of older classes of antimicrobials for human clinical use, with counterparts previously developed by animal health companies for use as growth promoters, has become common. Dr. Aarestrup of the Danish Veterinary Laboratory commented that "it will be necessary in the future to either totally avoid the use of antimicrobials for growth promotion or, once antimicrobials have been approved for growth promotion, to reserve these classes for growth promotion and search for therapeutic

options among other classes" (2). With respect to avilamycin, this latter option is the better one, now that everninomicin (and perhaps the entire orthosomycin class by extension) has been demonstrated to be unsafe for parenteral or injectable use in humans, because it allows animal producers to use a product that poses no resistance threat to public health. Finally, other unique antibiotics for treatment of serious gram-positive infections in humans (with no animal use counterparts) are in the pharmaceutical pipeline (e.g., LY333328 and daptomycin) or have recently been approved (e.g., linezolid). We hope that a fair balance can be achieved by the human medical and the animal health and production communities with regard to the types of antimicrobial agents that can be used in each sector.

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## References

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